AMENDMENTS TO THE CLAIMS

The version of the claims below replaces all prior versions of the claims:

1. (Currently amended) A method for modulating endothelial cell (EC) proliferation in a mammal, wherein the method comprises ~~increasing or~~ decreasing ezrin activity in the mammal by an amount sufficient to ~~modulate~~ promote proliferation of the cells by administering to the mammal an ezrin modulating agent before, during, or after the mammal is exposed to conditions conducive to damaging blood vessels.

2. (Original) The method of claim 1, wherein the ezrin activity is decreased by an amount sufficient to enhance the EC proliferation.

3. (Previously presented) The method of claim 1, wherein the method further comprises administering to the mammal at or near a site where modulation is desired at least one ezrin modulating agent sufficient to decrease the ezrin activity and enhance the EC proliferation.

4. (Withdrawn) The method of claim 3, wherein the ezrin modulating agent is a nucleic acid or at least one amino acid sequence.

5. (Withdrawn) The method of claim 4, wherein the amino acid sequence is a competitor of Tumor Necrosis Factor-alpha (TNF-α).

6. (Withdrawn) The method of claim 5, wherein the competitor is at least one of TNF soluble receptor protein (TNFsr), a TNF antagonist, anti-TNF antibody; or an effective fragment or derivative thereof.

7. (Withdrawn) The method of claim 4, wherein the ezrin modulating agent is an anti-sense nucleic acid, anti-ezrin antibody, or an effective fragment or derivative thereof.

8. (Original) The method of claim 3, wherein the ezrin modulating agent reduces or blocks activity of Rho kinase (ROCK-2) in the endothelial cells.

9. (Original) The method of claim 8, wherein the ezrin modulating agent is Y27632.

10. (Withdrawn) The method of claim 4, wherein the ezrin modulating agent is a nucleic acid encoding a dominantly and negatively acting fragment of mammalian ezrin; or an effective fragment or derivative of the protein.

11. (Original) The method of claim 1, wherein the decrease in ezrin activity is at least about 50% as determined by a standard cyclin A promoter binding assay.

12. (Original) The method of claim 1, wherein the decrease in ezrin activity is at least about 50% as determined by a standard ezrin mRNA stability assay.

13. (Original) The method of claim 2, wherein the decrease in ezrin activity is associated with a decrease in ezrin tyrosine phosphorylation as determined by a standard protein phosphorylation assay.

14. (Withdrawn) The method of claim 1, wherein the ezrin activity is increased in an amount sufficient to decrease the EC proliferation.

15. (Withdrawn) The method of claim 14, wherein the ezrin modulating agent is tumor necrosis factor (TNF) or an effective fragment thereof.

16. (Withdrawn) The method of claim 14, wherein the EC proliferation is decreased by at least about 20% as determined by a standard restenosis assay

17. (Currently amended) A method for inducing formation of new blood vessels in a mammal, the method comprising decreasing ezrin activity in an amount sufficient to induce formation of the new blood vessels in the mammal by administering to the mammal an ezrin modulating agent that decreases ezrin activity in mammalian cells <u>before, during, or after the mammal is exposed to conditions conducive to damaging blood vessels</u>.

18. (Original) The method of claim 17, wherein the method further comprises administering to the mammal at least one ezrin modulating agent sufficient to decrease ezrin DNA binding activity relative to a control.

19. (Original) The method of claim 18, wherein the ezrin modulating agent is an inhibitor of Rho kinase (ROCK-2).

20. (Withdrawn) The method of claim 18, wherein the ezrin modulating agent is a nucleic acid encoding a dominantly and negatively acting fragment of mammalian ezrin; or an effective fragment or derivative of thereof.

21. (Previously presented) The method of claim 18, wherein the method further comprises contacting endothelial cells (ECs) with the ezrin modulating agent thereby decreasing ezrin activity in the cells.

22. (Withdrawn) The method of claim 21, wherein the method further comprises transforming endothelial cells with the ezrin modulating agent under conditions conducive to expressing the agent and administering the transformed cells to the mammal.

23. (Withdrawn) The method of claim 22, wherein the ezrin modulating agent is a nucleic acid encoding a dominantly and negatively acting fragment of mammalian ezrin; or an effective fragment or derivative thereof.

24. (Original) The method of claim 17, wherein the mammal has, is suspected of having, or will have ischemic tissue.

25. (Original) The method of claim 24, wherein the tissue is associated with an ischemic vascular disease.

26. (Previously presented) The method of claim 1 or 17, wherein the method further comprises administering to the mammal at least one of an angiogenic protein, cytokine, hematopoietic protein , or an effective fragment thereof.

27. (Previously presented) The method of claim 26, wherein the angiogenic protein is acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF-1), epidermal growth factor (EGF), transforming growth factor α and β (TGF-α and TFG-β), platelet-derived endothelial growth factor (PD-ECGF), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNF-α), hepatocyte growth factor (HGF), insulin like growth factor (IGF), erythropoietin, colony stimulating factor (CSF), macrophage-CSF (M-CSF), angiopoetin-1 (Ang1) or nitric oxide synthase (NOS).

28. (Withdrawn) The method of claim 26, wherein the hematopoietic factor is granulocyte-macrophage colony-stimulating factor (GM-CSF), VEGF, Steel factor (SLF, also known as Stem cell factor (SCF)), stromal cell-derived factor (SDF-1), granulocyte-colony stimulating factor (G-CSF), HGF, Angiopoietin-1, Angiopoietin-2, M-CSF, b-FGF, and FLT-3 ligand.

29. (Withdrawn) The method of claim 28, wherein the protein is one of VEGF-B, VEGF-C, VEGF-2, VEGF-3; or an effective fragment thereof.

30. (Currently amended) A method for reducing the severity of blood vessel damage in a mammal, wherein the method comprises decreasing ezrin activity in endothelial cells (EC) before, during or after the mammal is exposed to conditions conducive to damaging the blood vessels[[ ]], wherein the decrease in ezrin activity is sufficient to reduce the severity of the blood vessel damage in the mammal by administering to the mammal an ezrin modulating agent that decreases ezrin activity in endothelial cells.

31. (Previously presented) The method of claim 30, wherein the method further comprises administering to the mammal at least one ezrin modulating agent sufficient to decrease ezrin DNA binding activity relative to a control.

32. (Original) The method of claim 31, wherein the ezrin modulating agent is injected at or near the site of blood vessel damage in the mammal.

33. (Original) The method of claim 32, wherein the ezrin modulating agent is an inhibitor of Rho kinase (ROCK-2).

34. (Original) The method of claim 33, wherein the ezrin modulating agent is Y27632.

35. (Withdrawn) The method of claim 30, wherein the ezrin modulating agent is a nucleic acid encoding a dominantly and negatively acting mammalian ezrin protein; or an effective fragment or derivative of the protein.

36. (Original) The method of claim 31, wherein the blood vessel damage is restenosis associated with an invasive manipulation or associated with ischemia.

37. (Original) The method of claim 36, wherein the invasive manipulation is balloon angioplasty, or deployment of stent or catheter.

38. (Original) The method of claim 37, wherein the stent is an endovascular stent.

39. (Original) The method of claim 36, wherein the ischemia is associated with at least one of infection, trauma, graft rejection, cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy, or myocardial ischemia.

40. (Original) The method of claim 30, wherein the ezrin modulating agent is administered to the mammal at least about 12 hours before exposing the mammal to the conditions conducive to damaging the blood vessels.

41. (Original) The method of claim 40, wherein the ezrin modulating agent is administered to the mammal between from about 1 to 10 days before exposing the mammal to the conditions conducive to damaging the blood vessels.

42. (Original) The method of claim 41, wherein the method further comprises administering the ezrin modulating agent to the mammal following the exposure to the conditions conducive to damaging the blood vessels.

43. (Withdrawn) A method for decreasing angiogenesis in a mammal, wherein the method comprises increasing ezrin activity in endothelial cells (ECs) of the mammal sufficient to decrease the angiogenesis.

44. (Withdrawn) The method of claim 43, wherein the method further comprises administering to the mammal at least one ezrin modulating agent sufficient to decrease ezrin DNA binding activity relative to a control.

45. (Withdrawn) The method of claim 44, wherein the ezrin modulating agent is injected at or near a site in which the decrease in angiogenesis is desired.

46. (Withdrawn) The method of claim 44, wherein the ezrin modulating agent is TNF Necrosis Factor alpha (TNF-α), Rho kinase; or an effective fragment or derivative thereof.

47. (Withdrawn) The method of claim 44, wherein the mammal has, is suspected of having, or is pre-disposed to develop cancer.

48. (Withdrawn) The method of claim 43, wherein the method further comprises administering at least one chemotherapeutic drug to the mammal.

49. (Withdrawn) A method for detecting a compound that modulates ezrin activity in the mammal, the method comprising the steps of:

1) introducing into cells a nucleic acid comprising at least part of a mammalian cyclin A gene linked to a detectable sequence,

2) adding at least one known or candidate ezrin modulating agent to the cells,

3) culturing the cells under conditions suited to expressing the nucleic acid and detecting the sequence in the presence and absence of the compound; and

4) determining the effect of the compound on the cells.

50. (Withdrawn) The method of claim 49, wherein step (4) of the method further comprises measuring at least one of proliferation and cycling of the cells.

51. (Withdrawn) The method of claim 49, wherein the nucleic acid used in the assay comprises a region spanning – 1200 to +250 of the mammalian cyclin A gene.

52. (Withdrawn) The method of claim 51, wherein the nucleic acid comprises a region spanning –924 to +100 of the mammalian cyclin A gene.

53. (Withdrawn) The method of claim 52, wherein the nucleic acid comprises at least one of the API, ATF, and CDE-CMR promoter sites.

54. (Withdrawn) The method of claim 53, wherein the nucleic acid comprises the CDE-CMR promoter site between about –79 to about +100 of the mammalian cyclin A gene.

55. (Withdrawn) The method of claim 49, wherein the nucleic acid comprises the human cyclin A protein gene promoter spanning about positions –79 to about +100 of the gene which promoter is covalently linked in-frame to a sequence encoding a fluorescent or phosphorescent protein; or a detectable fragment thereof.

56. (Withdrawn) The method of claim 55, wherein the label is derived from a fluorescent jellyfish protein.

57. (Withdrawn) The method of claim 56, wherein the jellyfish protein is green fluorescent protein (GFP) or red fluorescent protein (RFP).

58. (Withdrawn) The method of claim 49, wherein the nucleic acid comprises the human cyclin A protein gene promoter spanning about positions –79 to about +100 of the gene which promoter is covalently linked in-frame to a sequence encoding the luciferase or beta-galactosidase enzyme; or a detectable fragment thereof.

59. (Withdrawn) A method for detecting a compound that modulates ezrin activity, the method comprising the steps of:

1) adding at least one known or candidate ezrin modulating agent to the cells,

2) culturing the cells under conditions suited to increase or decrease ezrin phosphorylation relative to a control; and

3) identifying an increase or decrease in ezrin phosphorylation relative to a suitable control as being indicative of the compound.

60. (Withdrawn) The method of claim 59, wherein step (3) of the method comprises performing an immunoassay.

61. (Withdrawn) The method of claim 60, wherein the immunoassay comprises performing a sandwich type immunoassay with an anti-phosphotyrosine antibody.

62. (Withdrawn) A method for detecting DNA binding between ezrin (or a DNA binding fragment thereof) and at least part of a mammalian cyclin A gene, the method comprising the steps of:

1) incubating at least part of a mammalian cyclin A gene with the ezrin protein or a DNA binding fragment thereof, wherein the incubation is conducted under conditions sufficient to form a specific binding pair between the cyclin A gene and the ezrin protein (or fragment),

2) adding at least one known or candidate ezrin modulating agent to the incubation medium; and

3) detecting presence of a specific binding pair between the cyclin A gene (or fragment) and the ezrin protein (or fragment) in the presence and absence of the compound, wherein a reduction or absence of the binding pair is taken to be indicative of a compound that reduces or blocks ezrin binding to the cyclin A gene.

63. (Withdrawn) The method of claim 62, wherein the cyclin A gene part is a detectably-labeled oligonucleotide comprising at least the CDE-CDR sequence.

64. (Withdrawn) The method of claim 63, wherein the detectable label is visualized by means of an automated or semi-automated fluorescence, colorimetric, or phosphorescence detection device.

65. (Withdrawn) The method of claim 63, wherein the specific binding pair is detected by performing an electrophoretic manipulation.

66. (Original) The method of claim 1, 17, or 30, wherein the method further comprises isolating endothelial progenitor cells (EPCs) from the mammal and contacting the EPCs with at least one of: an ezrin modulating agent, cytokine, angiogenic factor or hematopoetic factor.

67. (Original) The method of claim 66, wherein the method further comprises administering the EPCs to the mammal in an amount sufficient to modulate endothelial cell proliferation.

68. (Original) The method of claim 67, wherein the method further comprises administering at least one of the following to the mammal before, during of after administration of the EPCs: ezrin modulating agent, cytokine, angiogenic factor or hematopoetic factor.

69. (Withdrawn) A pharmaceutical product for inducing neovascularization in a mammal, wherein the product comprises endothelial cells, the product comprising at least one ezrin modulating agent, wherein cells formulated to be physiologically acceptable to a mammal.

70. (Withdrawn) The pharmaceutical product of claim 69, wherein the product is sterile and further comprises at least one angiogenic protein or nucleic acid encoding the protein.

71. (Withdrawn) The pharmaceutical product of claim 70, wherein the endothelial cells express the ezrin modulating agent.

72. (Withdrawn) The pharmaceutical product of claim 71, wherein the expression is transient.

73. (Withdrawn) A kit for the introduction of a endothelial cells into a mammal, the kit comprising at least one ezrin modulating agent and optionally at least one angiogenic or hematopoietic protein or nucleic acid encoding same, the kit further

comprising a pharmacologically acceptable carrier solution, nucleic acid or mitogen, means for delivering the cells and directions for using the kit.

74. (Withdrawn) The kit of claim 73, wherein the means for delivering the endothelial cells is a stent, catheter or syringe.

75. (Previously presented) A method for increasing endothelial cell (EC) proliferation in a mammal, wherein the method comprises decreasing ezrin activity in the mammal by an amount sufficient to increase proliferation of the cells by administering to the mammal at or near a site where modulation is desired Y27632 sufficient to decrease the ezrin activity and enhance the EC proliferation.

76. (Previously presented) A method for reducing the severity of blood vessel damage in a mammal, wherein the method comprises decreasing ezrin activity in endothelial cells (EC) before, during or after the mammal is exposed to conditions conducive to damaging the blood vessels, wherein the decrease in ezrin activity is sufficient to reduce the severity of the blood vessel damage in the mammal by administering to the mammal Y27632 at or near the site of blood vessel damage sufficient to decrease ezrin DNA binding activity relative to a control.

77. (Previously presented) The method of claim 1, wherein the endothelial cells have been contacted with TNF-α.

78. (Previously presented) The method of claim 21, wherein the endothelial cells have been contacted with TNF-α.

79. (Previously presented) The method of claim 30, wherein the endothelial cells have been contacted with TNF-α.

80. (Currently amended) The method of claim 30,[[.]] wherein blood vessel damage is associated with inflammation.

81. (Previously presented) The method of claim 1, wherein ezrin activity is increased or decreased by contacting endothelial cells *ex vivo* with an ezrin modulating agent.

82. (Currently amended) The method of claim 21, wherein the endothelial cells are contacted *ex vivo* with an ezrin modulating agent.

83. (Previously presented) The method of claim 30, wherein ezrin activity is decreased by contacting endothelial cells *ex vivo* with an ezrin modulating agent.